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Stereoretentive Olefin Metathesis: An Avenue to Kinetic Selectivity

T. Patrick Montgomery, Tonia S. Ahmed, and Robert H. Grubbs*

Abstract: Olefin metathesis is an incredibly valuable transformation that has gained widespread use in both academic and industrial settings. Lately, stereoretentive olefin metathesis has garnered much attention as a method for the selective generation of both *E*- and *Z*-olefins. Early studies employing ill-defined catalysts showed evidence for retention of the starting olefins at early conversion. However, thermodynamic ratios were reached as the reaction proceeded to equilibrium. Recent studies in olefin metathesis have focused on the synthesis of catalysts that can overcome the inherent thermodynamic preference of an olefin, providing synthetically useful quantities of a kinetically favored olefin isomer. These reports have led to the development of stereoretentive catalysts that not only generate *Z*-olefins selectively, but also kinetically produce *E*-olefins, a previously unmet challenge in olefin metathesis. Advancements in stereoretentive olefin metathesis using tungsten, ruthenium, and molybdenum catalysts are presented.

1. Introduction

Olefin metathesis has become an indispensable method for the formation of carbon–carbon double bonds,[1–5] finding use in synthetic organic,[6–8] biological,[9–11] and materials chemistry.[12–14] The ubiquity of olefin metathesis as a synthetic tool has been linked to the evolution of catalysts from ill-defined mixtures to well-characterized molecular species based on molybdenum, ruthenium and tungsten. This transformation proceeds through a [2+2] cycloaddition between a metal-carbene and an olefin to generate a metallacyclobutane intermediate (Scheme 1).[15] Cycloreversion can occur to release both a new olefin species and metal carbene. The orientation of the substituents on the metallacyclobutane intermediate is critical for determining stereoselectivity; thus, controlling the geometry of this intermediate is necessary for achieving both stereoselective and stereoretentive metathesis.

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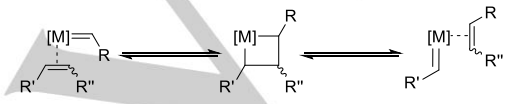


Scheme 1. Accepted mechanism of olefin metathesis.

Typically, metathesis using early well-defined catalysts is non-selective: the geometry of the products represents the thermodynamic ratio of olefin isomers. A kinetically selective process is required to overcome this thermodynamic preference for olefin geometry. The first examples of kinetically *Z*-selective processes were reported by Schrock, Hoveyda, and coworkers, identifying both molybdenum- and tungsten-based systems to perform this transformation, which generated the desired *Z*-olefins in high selectivity.[16–26] A large aryloxy-moiety shields one side of the catalyst, forcing the substituents on the generated metallacyclobutane to be all *syn* (Figure 1 (a)). Later, Grubbs and coworkers introduced a highly efficient, *Z*-selective olefin metathesis catalyst that utilized a cyclometalated ruthenium-carbene species.[27–36] The aryl group on the *N*-heterocyclic carbene (NHC) forces all the substituents on the ruthenacycle *syn* (Figure 1 (b)). Subsequent reports by the Jensen[37–39] and Hoveyda[40–43] groups also described *Z*-selective ruthenium catalysts. These catalysts relied on successfully controlling the orientation of the metallacyclobutane substituents as well.

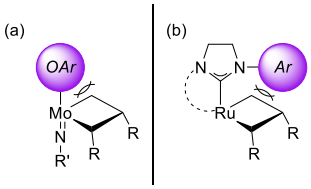


Figure 1. General model for *Z*-selectivity. (a) Model for *Z*-selectivity when using molybdenum catalysts. (b) Model for *Z*-selectivity when using cyclometalated ruthenium catalysts.

An unmet challenge in olefin metathesis is the development of a kinetically *E*-selective process. Thermodynamic properties of a metathesis normally favor formation of the *E*-isomer, but in some cases the energy difference between *E*- and *Z*-olefins can be quite small or even favors formation of the *Z*-isomer.[44] Alkyne metathesis followed by stereoselective semireduction represents a reliable method for the stereoselective formation of *E*-olefins,[45] but a multi-step protocol is not desired. A recent study from Grubbs and coworkers indicated that a catechothiolate-modified ruthenium catalyst could be used to generate *E*-olefins selectively when employing *E*-olefins as the reactants.[46] This represented the earliest case of a kinetically *E*-selective metathesis. The idea of stereoretentive olefin metathesis to kinetically generate both *E*- or *Z*-olefins has shown great promise of late and has encouraged the synthesis of new metathesis catalysts. This minireview will focus on the development of stereoretentive olefin metathesis catalysts and their application to generate products of both *E*- or *Z*-isomers for small molecule synthesis. Although important, stereoretentive olefin metathesis reactions to generate polymers will not be discussed in this report.

Patrick Montgomery received his B.S. degree in Chemistry from the University of Alabama in 2010. He then joined the group of Prof. Michael Krische at the University of Texas at Austin, where he studied carbonyl addition chemistry using transfer hydrogenation. Upon obtaining his Ph. D. in 2015, Patrick moved to the group of Prof. Robert Grubbs at the California Institute of Technology where he is currently developing new olefin metathesis catalysts.

Tonia Ahmed received B.S. degrees in Chemistry and Mathematics from West Virginia University in 2013. During her undergraduate studies, she conducted research under the guidance of Prof. George O'Doherty and Prof. Xiaodong Michael Shi at WVU and under Prof. John Bercaw as a Summer Undergraduate Research Fellow at the California Institute of Technology. She is currently a Ph.D. candidate in the lab of Prof. Robert Grubbs at the California Institute of Technology working broadly on ruthenium metathesis catalyst development and in the synthesis of small molecules and polymers.

Robert Grubbs is the Victor and Elizabeth Atkins Professor of Chemistry at the California Institute of Technology. His group studies and develops new organometallic complexes and evaluates their performance in both polymer and synthetic applications.

2. Evidence of Stereoretention

Early studies employing ill-defined metathesis catalysts were conducted to gain a better understanding of the metallacycle intermediate.[47] These investigations were aimed at exploring the stereochemistry of the metallacycle and how it may affect the stereochemistry of the olefin products. As various olefins were examined, it was reported that the stereochemistry of the reactant olefin could sometimes influence the stereochemistry of the product, even when using the same catalyst for either *E*- or *Z*-olefins. Stereoretention was detected at early conversion where the ratio of *E*:*Z* isomers was different than what is observed as the equilibrium ratio. Although important for deciphering the reactive intermediate in olefin metathesis, these findings also provided early inspiration for stereoretentive olefin metathesis. The catalytic systems discussed in this section showed some evidence of the products retaining the starting olefin's geometry at early conversion, but equilibration to the thermodynamic ratio of *E*:*Z* was rapid.

2.1. Early Tungsten Catalysts Showing Stereoretention

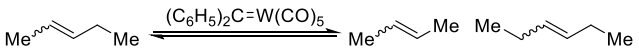
Many of the early observations for stereoretention in olefin metathesis were made using tungsten catalysts.[48–56] One report from Calderon and coworkers examined WCl_6/EtOH/$EtAlCl_2$ in the self-metathesis of 2-pentene.[48] They noted that when using *cis*-2-pentene, early conversion indicated preferential formation of both *cis*-2-butene and *cis*-3-hexene, which quickly began to approach the equilibrium ratio (the observed equilibrium ratios of 2.6:1 *E*:*Z* and 6.2:1 *E*:*Z* respectively). A similar trend was observed when using *trans*-2-pentene, with the products being formed initially in high *trans*-content then reaching the thermodynamic ratio of *E*:*Z* isomers as conversion increased.

Basset and coworkers studied the self-metathesis of *cis*-2-pentene employing various tungsten precatalysts in combination with $EtAlCl_2$.[49] When using $W(CO)_5P(n\text{-}Bu)_3$/$EtAlCl_2$ in the self-metathesis of *cis*-2-pentene, early conversion indicated 2-butene was formed in 0.76:1 *E*:*Z*, and 3-hexene was formed in 0.83:1 *E*:*Z*, which are different from the thermodynamic ratios. Additional studies from Basset and coworkers involved depositing various hexavalent tungsten precatalysts onto an alumina support. These catalysts provided a higher rate of stereoretention when performing the self-metathesis of *cis*-2-pentene, furnishing 2-butene in 0.37:1 *E*:*Z*.[49,50] It is believed that the higher levels of stereoretention at early conversion for the supported catalysts are due to the more defined steric environment dictated by the alumina surface. These ligand effects on stereoretention are also noted when comparing $W(CO)_4Br_2$ and $W(CO)_4Cl_2$, with the bromide catalyst providing 2-butene in 0.5:1 *E*:*Z* to 0.69:1 *E*:*Z* for the chloride catalyst.[50]

Katz and coworkers were able to improve the rate of stereoretention in the self-metathesis of 2-pentene when using well-defined precatalyst $(C_6H_5)_2C{=}W(CO)_5$.[51] Levels of stereoretention in the self-metathesis of *cis*-2-pentene employing $(C_6H_2)_2C{=}W(CO)_5$ were high at early conversion, providing 2-butene as 94% *cis* and 3-hexene as 93% *cis* (Table 1, entry 1). For previous catalytic systems, they believed the presence of metal halides could behave as Lewis acids, facilitating the cleavage of a carbon-metal bond in the metallacyclobutane and furnish the 3-metalla-propyl cation which can perform bond rotations, scrambling the geometry of the olefin.[57] The stereoretention observed in the self-metathesis of *trans*-2-pentene was not as great as what was seen with *cis*-2-pentene (Table 1, entry 2), with the *E*:*Z* ratios being similar to the observed equilibrium ratios. However, it was thought that these are true properties of stereoretention at early conversion, in which there was negligible isomerization of the *trans*-2-pentene starting olefin (Table 1, entry 2). Improvements on the stereoretention of *trans*-olefins was made using

$W(CO)_6/CCl_4/h\nu$.[52] Garnier and coworkers reported the self-metathesis of *trans*-olefins (2-pentene, 2-hexene, and 2-heptene) provided 2-butene in more than 95% *trans*.

Table 1. Evidence of stereoretention observed in the self-metathesis of 2-pentene using $(C_6H_5)_2C{=}W(CO)_5$.



		% *cis*-olefin at early conversion		
Entry	Starting Olefin	2-butene	2-pentene	3-hexene
1	*cis*-2-pentene	94	96	93
2	*trans*-2-pentene	27	<1	17

Ofstead and coworkers evaluated the self-metathesis of 4-methylpent-2-ene with $WCl_6/Bu_4Sn/Et_2O$, arguing that simple linear alkenes such as 2-pentene have a limited ability to reveal key aspects of olefin metathesis because of their lack of steric bulk.[55] Interestingly, they did observe some degree of stereoretention in the formation of 2-butene at early conversion (Figure 2). However, 2,5-dimethyl-3-hexene was always formed with exceptional levels of *trans*-selectivity, due to the large groups residing equatorial on the metallacyclobutane.[47,55] Ultimately, they concluded that retention of stereochemical configuration of an olefin through metathesis was not a general feature of olefin metathesis, thus more selective catalysts must be designed.

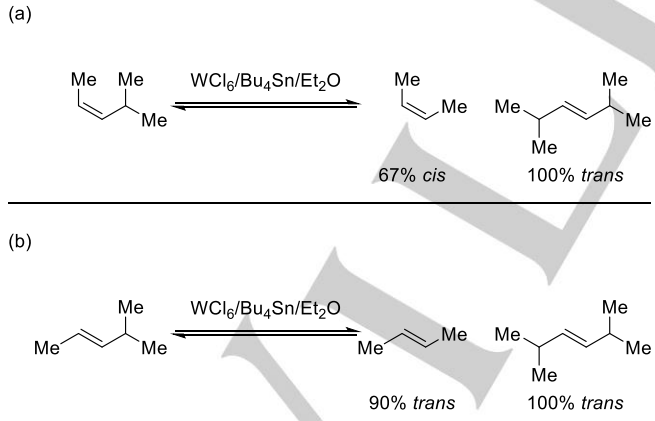


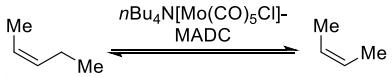
Figure 2. Stereochemical observations in the self-metathesis of 4-methylpent-2-ene at early conversion. (a) Results using the *cis*-isomer. (b) Results using the *trans*-isomer.

2.2. Early Molybdenum Catalysts Showing Stereoretention

As with tungsten, molybdenum-based catalysts provided some indication that olefin metathesis could be rendered stereoretentive. One of the early reports of stereoretentive olefin metathesis was made by Hughes, in which he employed $py_2Mo(NO)_2Cl_2/EtAlCl_2$ as the catalytic system in the self-metathesis of 2-pentene.[58] At early conversion, Hughes noticed the catalyst provided the products with preferential retention for the starting olefin geometry. When performing self-metathesis on *cis*-2-pentene, 2-butene and 3-hexene were generated with 0.22:1 and 0.43:1 *E*:*Z* respectively. Conversely, when using *trans*-2-pentene, 2-butene and 3-hexene were furnished as 10:1 and >10:1 *E*:*Z* respectively.

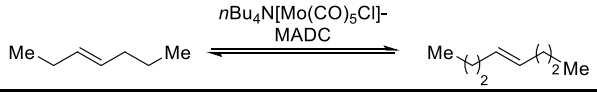
Doyle probed rates of stereoretention using various molybdenum complexes with the form $R_4N[Mo(CO)_5X]$.[59] He ultimately examined $n Bu_4N[Mo(CO)_5Cl]/MeAlCl_2$ in the self-metathesis of 2-pentene and found that this catalytic system behaved similarly to that reported by Hughes (*vide supra*). Self-metathesis of *cis*-2-pentene showed high stereoretention at early conversion, but as the metathesis reached equilibrium over time, the thermodynamic ratio dominated (Table 2). The same trend was observed using *trans*-3-heptene. As the self-metathesis of *trans*-3-heptene proceeded, the stereochemical distribution of the product moved from highly stereoretentive to the equilibrium ratio (Table 3).

Table 2. Equilibration of the self-metathesis of *cis*-2-pentene over time.



		Z:*E* ratio	
Entry	Time (min)	2-butene	2-pentene
1	1.5	1.1:1	7.0:1
2	2.5	0.83:1	1.6:1
3	5	0.48:1	0.36:1
4	8	0.42:1	0.30:1
5	10	0.40:1	0.28:1
6	120	0.40:1	0.22:1

Table 3. Equilibration of the self-metathesis of *trans*-3-heptene over time.



		E:*Z* ratio	
Entry	Time (min)	3-heptene	4-octene
1	0	98:1	n/a
2	2	50:1	18:1
3	5	28:1	15:1
4	8	19:1	10:1
5	11	11:1	9.4:1
6	15	8.3:1	7.9:1
7	25	6.4:1	5.0:1
8	120	4.6:1	3.7:1

Along with their investigations into tungsten catalysts, Basset and coworkers also examined molybdenum-based systems.[53] Using $Mo(NO)_2Cl_2(PPh_3)_2$,[60,61] they found that the self-metathesis of 2-pentene provided 2-butene with much higher levels of stereoretention than for tungsten catalysts at early conversion. The self-metathesis of *cis*-2-pentene provided 2-butene in 0.2:1 *E*:*Z*, while the self-metathesis of the *trans*-isomer provided 2-butene in 12.5:1 *E*:*Z*. They proposed that the levels of stereoretention were higher for molybdenum because molybdenum-based catalysts form shorter molybdenum–carbon bonds in the metallacyclobutane. This results in decreased distance between C_2 and C_4 in the metallacycle; consequently, there would be more 1,3-diaxial interaction between substituents attached to those carbons.

Tanaka and coworkers developed a MoO_x/β-TiO_2 catalysts that was resistant to hydrogen scrambling.[62] They used this catalyst to examine the cross metathesis between *cis*-2-butene and *cis*-2-butene-d_8 and found 2-butene-d_4 was formed in more than 60% *cis* at early conversion. When evaluating the *trans*-isomers in this transformation, they also found high stereoretention at early conversion, with greater than 90% of the *trans*-isomer being formed.

3. Stereoretentive Metathesis Using Tungsten

The discovery of well-defined catalysts enabled the design and synthesis of new scaffolds to investigate reactivity and selectivity. Although research on metathesis catalysts has largely centered on ruthenium- and molybdenum-based systems, useful and interesting tungsten catalysts have been unveiled. Furthermore, some examples of stereoretentive tungsten-based olefin metathesis catalysts are reported.

One tungsten catalyst that is known to promote stereoretentive olefin metatheses is the cyclometalated aryloxy-based system **1** described by Basset and coworkers (Figure 3).[63–67] This catalyst displayed good activity in the self-metathesis of 2-pentene, and exhibited excellent stereoretention.[63] When performing the self-metathesis of *cis*-2-pentene, the predominant isomer of 2-butene formed is *cis*, even when reaction equilibrium is reached (Figure 3 (a)). Likewise, *trans*-2-pentene also showed high stereoretention with catalyst **1** Upon reaching reaction equilibrium, *trans*-2-butene is

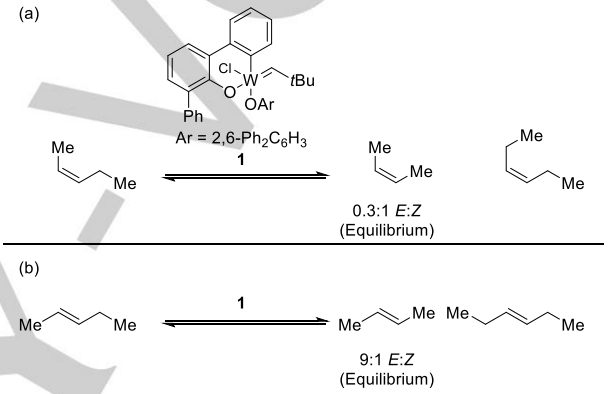


Figure 3. Catalyst **1** as a stereoretentive olefin metathesis catalyst in the self-metathesis of 2-pentene. (a) Catalyst **1** shows stereoretention of *cis*-2-pentene a equilibrium conversion. (b) Catalyst **1** shows stereoretention of *trans*-2-pentene a equilibrium conversion.

formed in 9:1 *E*:*Z* (Figure 3 (b)).[63] It is believed that the steric environment created by the cyclometalated-aryloxy group favors the formation of metallacyclobutane with substituents at C_2 and C_4 positions equatorial for the metathesis of *cis*-olefins (Figure 4 (a)) and a metallacyclobutane with all substituents equatorial for the metathesis of *trans*-olefins (Figure 4 (b)). This catalyst was recently shown to catalyze the self-metathesis of sterically hindered olefins with high stereoretention (Scheme 2).[67] Incredibly, even at high conversion, *cis*-olefin **3** was favored in 2:1 *Z*:*E*. Following these results, **1** was employed in the synthesis of *cis*-combretastatin A-4, a potent chemotherapy agent which functions as a tubulin polymerization inhibitor.[68–76]

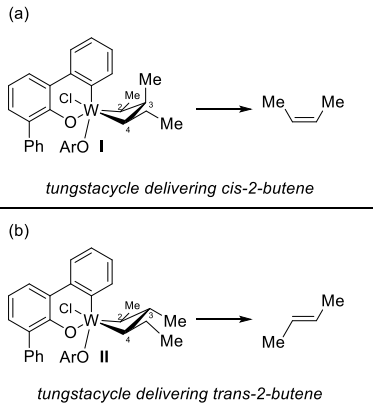
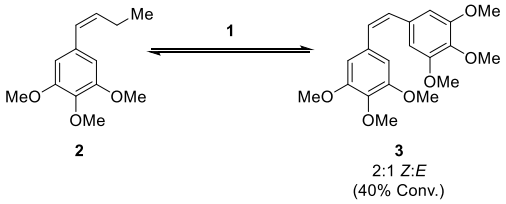


Figure 4. Favored tungstacycles to generate 2-butene. (a) Favored tungstacycle furnishing *cis*-2-butene from the self-metathesis of *cis*-2-pentene. (b) Favored tungstacycle to generate *trans*-2-butene from the self-metathesis of *trans*-2-pentene.



Scheme 2. Evaluation of **1** in stereoretentive self-metathesis to generate sterically encumbered *Z*-olefin **3**.

4. Stereoretentive Metathesis

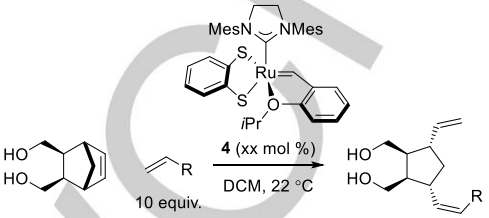
Using Ruthenium

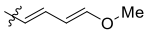
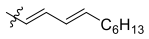
Ruthenium-based olefin metathesis catalysts have become essential in the synthesis of complex molecules and materials. These catalysts are exceptionally tolerant of air, moisture, and a wide variety of functional groups.[2] This has enabled their widespread use in numerous applications. Recent studies using ruthenium-based olefin metathesis catalysts have succeeded at developing *Z*-selective ruthenium catalysts.[28,29,77] One of these systems, using ruthenium catalysts bearing catechothiolate ligands, used stereoretention to provide *Z*-olefins. Additional investigations revealed this catalyst to also kinetically generate *E*-olefins.

4.1. *Z*-Selectivity Through Stereoretention

Initial studies in stereoretentive olefin metathesis to generate *Z*-olefins made use of a catechothiolate-modified ruthenium catalyst (**4**) for ring-opening cross metathesis (ROCM).[40–42] Catalyst **4** performed ROCM of norbornenes and a variety of terminal olefins, displaying good reactivity with styrenes, functionalized carbon chains, and dienes (Table 4).

Table 4. ROCM of norbornene diols with terminal olefins using **4**.



Entry	R	**4** (xx mol %)	Time (h)	Yield (%)	*Z* (%)
1	Ph	1	1	92	97
2	*m*-FC_6H_4	1	1	93	96
3	$(CH_2)_2OTBS$	5	8	68	>98
4	$(CH_2)_2C(O)NHPh$	5	8	65	>98
5		2	2	84	91
6		5	2	80	>98

*Entries 1 and 2 conducted in THF.

The Hoveyda group also evaluated **4** in the cross metathesis of *cis*-2-butene-1,4-diol and allylbenzene.[43] Catalyst **4** furnished the desired product in high *Z*-selectivity (98:2 *Z:E*), but poor yield (42% Yield). Migratory insertion of the propagating carbene into the ruthenium-sulfur bond *trans* to the NHC was a proposed decomposition pathway (Figure 5). Computational studies indicated incorporation of electron-withdrawing substituents to the catechothiolate would increase catalyst stability by reducing the electron density on the sulfur atoms. This would weaken their *trans* influence and make the ruthenium-sulfur bond more stable. Based on

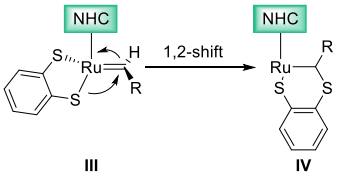


Figure 5. Potential catalyst decomposition pathway for **III**, occurring *via* insertion of the carbene into the ruthenium-sulfur bond.

these findings, catalysts **5**-**8** were synthesized. They catalyzed the cross metathesis of *cis*-2-butene-1,4-diol and allylbenzene, delivering high *Z*-selectivity and moderate yields (Figure 6). Although the reactivities and selectivities were similar, **5** has the benefit of being synthesized from commercially available 3,6-dichloro-1,2-benzenedithiol. The catalytic

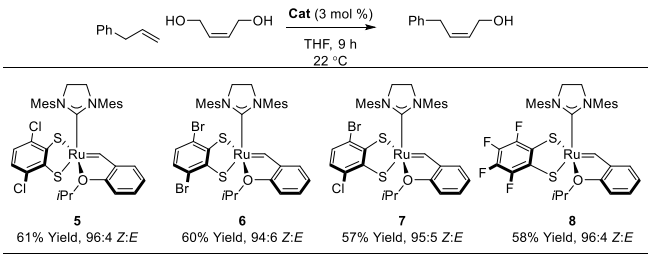


Figure 6. Ruthenium-catalyzed cross metathesis of allylbenzene and *cis*-2-butene-1,4-diol employing electron deficient dithiolate ligands.

efficiency of **5** was evaluated across a wide substrate scope. *Cis*-2-butene-1,4-diol participated in cross metathesis with functionalized carbon chains (esters, aldehydes, and acids), styrenes, and dienes (Figure 7). Additionally, stereoretentive cross metathesis of readily available olefins such as oleyl alcohol and oleic acid with *cis*-2-butene-1,4-diol proceeded well, delivering high-value products.[78]

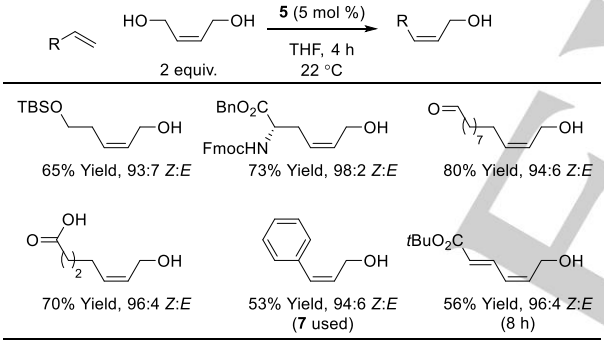


Figure 7. Employment of **5** in cross metathesis to generate *Z*-allyl alcohols *via* stereoretention.

4.2. *E*-Selectivity Through Stereoretention

Catalyst **5** proved to be a suitable catalyst for stereoretentive *Z*-selective metathesis. Upon further study of this catalysts by scientists at Materia Inc. and in the Grubbs group, it was observed that self-metathesis of *trans*-5-tetradecene generated *trans*-5-decene in 95:5 *E*:*Z*.[46] This was the first report of a highly *E*-selective metathesis through kinetic control. The proposed model for this discovery is based on a "side-bound" metallacyclobutane intermediate in which the substituents at C_2 and C_4 are forced down and away from the *N*-aryl groups of the NHC (Figure 8). The substituent at C_3, however, can point up or down, depending on the stereochemistry of the starting material due to the presence of the open space between the two *N*-aryl groups and in front of the imidazole-2-ylidene ring. Beginning with a *cis*-olefin, this substituent is predisposed to point down (Figure 8 (a)). However, this substituent points up if the reacting olefin has *trans*-stereochemistry (Figure 8 (b)). As expected from the model, *E*-substrates were less reactive due to the steric congestion in the *trans*-metallacycle.

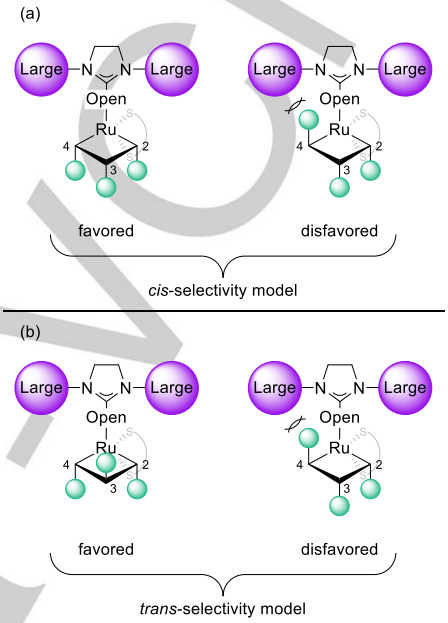
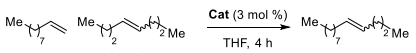
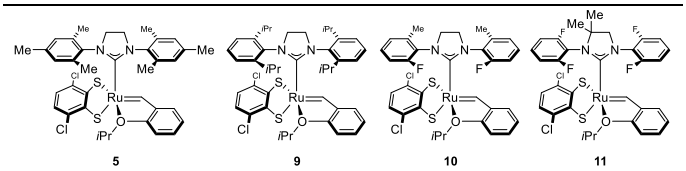


Figure 8. Models for stereoretention using ruthenium olefin metathesis catalysts modified by catechothiolate ligands. (a) Stereochemical model for *cis*-selectivity. (b) Stereochemical model for *trans*-selectivity.

It was believed that reducing the size of the *ortho*-substituents on the *N*-aryl group of the NHC would lead to a catalyst that could better accommodate *trans*-olefins. A series of catalysts (**9**-**11**) were synthesized, varying the size of the *ortho*-substituents of the *N*-aryl rings (Table 5). A general trend was seen upon reaction with *trans*-olefins in which reactivity increased with decreasing size of *ortho*-substituents (**9** < **5** < **10** < **11**) (Table 5, entries 1-4). The open space between the two *N*-aryl groups increases as the *ortho*-substituent size decreases, thus further supporting the proposed stereochemical model of the metallacyclobutane intermediate in which the C_3 substituent needs to point up in reactions with *trans*-olefins. A similar trend was observed when reacting internal olefins such as *trans*-1,4-diacetoxy-but-2-ene and *trans*-4-octene: as the *ortho*-substituents on the *N*-aryl groups get smaller, yield of the desired product increased, while maintaining exceptional selectivity (>99:1 *E*:*Z*). Interestingly, the reactivity of these catalysts with *cis*-olefins decreased as the *ortho*-substituents got smaller (**11** < **10** < **5** < **9**) (Table 5, entries 5-8).

Table 5. Stereoretentive metathesis of 1-decene and 4-octene.

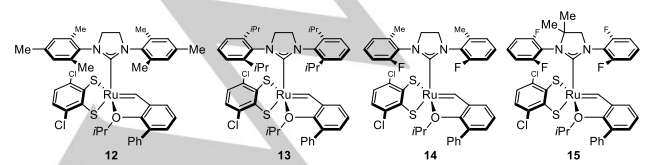




Entry	Octene	Cat	Yield (%)	*Z*:*E*
1	*trans*	**9**	4	13:88
2	*trans*	**5**	7	<1:99
3	*trans*	**10**	29	<1:99
4	*trans*	**11**	31	<1:99
5	*cis*	**9**	74	96:4
6	*cis*	**5**	58	>99:1
7	*cis*	**10**	57	97:3
8	*cis*	**11**	54	>99:1

Although *Z*-selective cross metathesis involving catalysts **5**, **9**-**11** was selective and high yielding when using *cis*-olefins, the corresponding reactions with *trans*-olefins were significantly slower and generated poor yields of products, especially in reactions with terminal olefins. In the presence of terminal olefins, a ruthenium methylidene species can be generated, which is susceptible to insertion of the ruthenium sulfur bond, rendering the catalyst inert (a similar process is proposed in Figure 5).[43]

Continuing investigations into the catechothiolate-based ruthenium catalysts revealed that a large contributing factor to this lack of activity in reactions involving *trans*-olefins was due to poor catalyst initiation with *trans*-olefins.[79] Replacing the 2-isopropoxybenzylidene ligand with a 3-phenyl-2-isopropoxybenzylidene ligand, a modification that is known to increase initiation rates of ruthenium metathesis catalysts,[80–83] resulted in the synthesis of a series of fast-initiating catalysts



	12	13	14	15
k_Z/k_E	60	200	7.5	4

Figure 9. Series of fast-initiating catalysts synthesized and their relative rate constants k_Z/k_E. Reprinted with permission from T. S. Ahmed, R. H. Grubbs, *J. Am. Chem. Soc.* **2017**, *139*, 1532–1537. Copyright 2017 American Chemical Society.

chelating group, initiates much faster than **5** (Figure 10). While it takes more than 24 hours for 85% of **5** to initiate, **12** is almost completely initiated after only 3 hours. *Trans*-selective cross

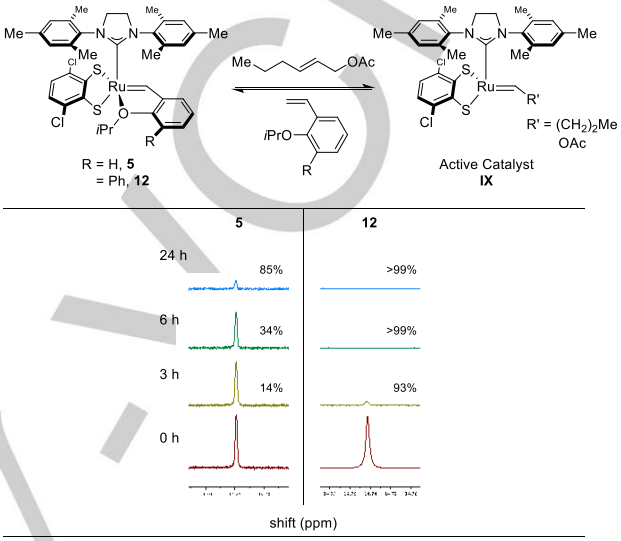


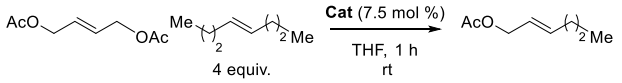
Figure 10. Studies on the initiation rates of **5** and **12** in the presence of *trans*-2-hexenyl acetate. Reprinted with permission from T. S. Ahmed, R. H. Grubbs, *J. Am. Chem. Soc.* **2017**, *139*, 1532–1537. Copyright 2017 American Chemical Society.

metathesis with **12**-**15** was completed in minutes or hours rather than the multiple days required for catalyst **5**. A comparison of the relative rates of reactions with *Z*- and *E*-olefins was conducted using the self-metathesis of methyl oleate. The relative rate constant (k_Z/k_E) for each catalyst was calculated using the time required (t_Z and t_E) for the self-metathesis of each isomer to reach equilibrium using a specific catalyst (Eq. 1). First-order kinetics were assumed with respect

$$k_Z/k_E = [\mathrm{Ru}]_E t_E/([\mathrm{Ru}]_Z t_Z) \quad (1)$$

to initial catalyst concentration (Figure 9). Again, a similar trend with respect to the *ortho*-substituents on the *N*-aryl group of the NHC showed that as the *ortho*-substituent gets smaller (**13** < **12** < **14** < **15**), reactivity with *trans*-olefins increases (Figure 9). One of the most pronounced effects of utilizing this larger chelating group was observed in the cross metathesis of *trans*-1,4-diacetoxy-2-butene and *trans*-4-octene. With the previous generation of stereoretentive ruthenium metathesis catalyst (**5**), this transformation was problematic, delivering the desired olefins in poor yield after one hour (Table 6, entry 1); however, employment of **12**-**15** in this transformation provided the desired olefin in much higher yield after only one hour, while maintaining exceptional *E*-selectivity (Table 6, entries 2-5). Additional investigations of **12**-**15**'s tolerance for terminal olefins using the cross metathesis of 1-decene and 4-octene revealed similar activities and selectivities observed in Table 5.

Table 6. Stereoretentive cross metathesis of *trans*-1,4-diacetoxy-2-butene and *trans*-4-octene.



Entry	Cat	Yield (%)	*E*:*Z*
1	**5**	4	n/a
2	**12**	23	>99:1
3	**13**	2	>99:1
4	**14**	83	>99:1
5	**15**	41	>99:1

5. Stereoretentive Metathesis Using Molybdenum

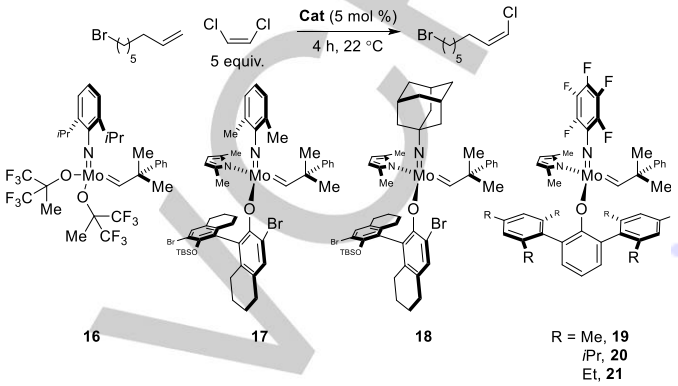
Molybdenum-based olefin metathesis catalysts were some of the first catalysts investigated in the early stages of this field.[84,85] Since, many breakthroughs in olefin metathesis have been made using molybdenum catalysts. Recent advancements have built on the catalytic structure of *Z*-selective systems[16–22] and have provided access to valuable products through stereoretentive olefin metathesis.

5.1. *Z*-Selectivity Through Stereoretention

Initial studies into stereoretentive olefin metathesis using molybdenum catalysts were driven by the desire to obtain access to alkenyl halides through the direct cross metathesis of terminal olefins and halo-substituted olefins.[86] The synthesis of alkenyl halides is inefficient, and methods for the stereoselective synthesis of *Z*-alkenyl halides are even more limited.[87–94] Unfortunately, the development of a catalyst to perform cross metathesis with alkenyl halides was challenging. Ruthenium metathesis catalysts proved to be less stable in the presence of alkenyl halides, due to the formation of Fischer-type carbenes and catalyst decomposition, requiring high catalyst loadings for good yields.[95–97]

Studies in the cross metathesis of alkenyl halides from Schrock, Hoveyda, and coworkers commenced using the cross metathesis system of 8-bromo-1-octene and *Z*-1,2-dichloroethene (Table 7). Catalysts **16** and **17** provided minimal desired product (Table 7, entries 1 and 2), showing preference for the cross metathesis of the terminal olefin. Catalyst **18**, a well characterized *Z*-selective catalyst,[16,19,22] furnished the desired product in low yield but with high *Z*-selectivity (Table 7, entry 3). Further modification to the imido and aryloxy groups delivered catalysts (**19**-**21**), which performed the cross metathesis much more efficiently (Table 7, entries 4-6). It is believed that the *m*-terphenyl-based aryloxy group provides the necessary steric demands for catalytic robustness, reactivity, and selectivity. No *E*-isomer was detected using this method.

Table 7. Catalysts assayed in cross metathesis to form alkenyl chlorides.



Entry	Cat	Yield	*Z*:*E*
1	**16**	<5	n/a
2	**17**	<5	n/a
3	**18**	27	>98:2
4	**19**	60	>98:2
5	**20**	40	98:2
6	**21**	75	>98:2

Entry 6 was used 3 mol % **21**.

Catalyst **21** was assayed across a wide substrate scope using *Z*-1,2-dichloroethene as the metathesis partner, delivering functionalized aliphatics, alkynes, and heteroaromatic products (Figure 11). Further evaluation of **21** employed 1,2-dibromoethene as the metathesis partner. Pure *Z*-1,2-dibromoethene is difficult to obtain, so a 64:34 *Z*:*E* mixture (commercially available) was used. *Z*-alkenyl bromide products were formed in good yields and with good levels of *Z*-selectivity (Figure 11), albeit lower than what was observed for the formation of *Z*-alkenyl chlorides. The reduced *Z*-selectivity is attributed to the incorporation of *E*-1,2-dibromoethene as a cross metathesis partner.

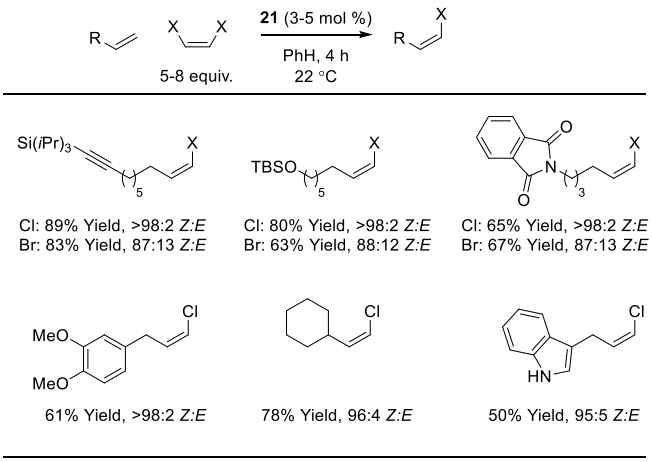


Figure 11. Employment of **21** in the formation of *Z*-alkenyl chlorides and bromides via stereoretentive cross metathesis.

Z-alkenyl fluorides could also be generated using **21**. Fluorinated molecules have seen widespread application in both the pharmaceutical and agrochemical industries due to their useful properties: improved metabolic stability, enzyme binding, and lipophilicity.[98,99] However, 1,2-difluoroethene has a low boiling point and is explosive, so a practical fluorine source was needed. *Z*-1-Bromo-2-fluoroethene was identified as a useful alkenyl fluoride source, but the unsymmetrical olefin could create a selectivity problem. It was reasoned that the fluoro-products would be favored. ^{1}H NMR revealed that H_{Br} was more upfield than H_F, indicating an electron polarization of the olefin (Figure 12 (a)). This would favor approach of the electrophillic molybdenum center to the carbon attached to the bromide over the carbon attached to the fluoride (which should be more electron–deficient). Additionally, fluoride is a smaller substituent than bromide, so steric clash between the fluoride and the R group on the alkylidene is minimal, delivering the desired regioselectivity in the metallacyclobutane (Figure 12 (b)).

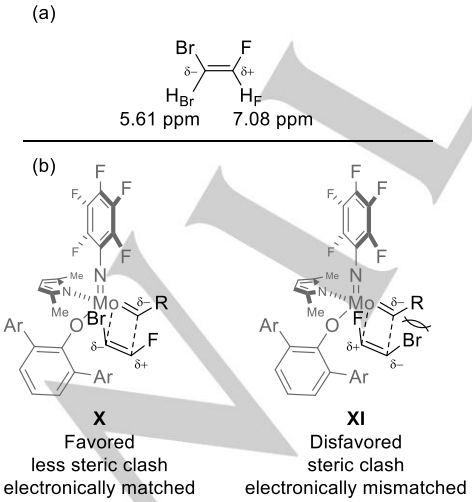


Figure 12. Rationalization for the selectivity in the formation of *Z*-alkenyl fluorides. (a) Electronic observations for *Z*-bromo-fluoroethene. (b) Steric and electronic effects in the formation of the metallacycle intermediate.

Results consistent with these hypotheses were obtained in the cross metatheses of terminal olefins and *Z*-1-bromo-2-fluoroethene with **21**. This system displayed good tolerance for functionalized carbon chains and aromatic systems (Figure 13). Though the bromo-product was generated, this pathway can be minimized by increasing the steric demands of the R group on the terminal olefin. Further employment of this methodology to complex molecules was also achieved (Figure 13).

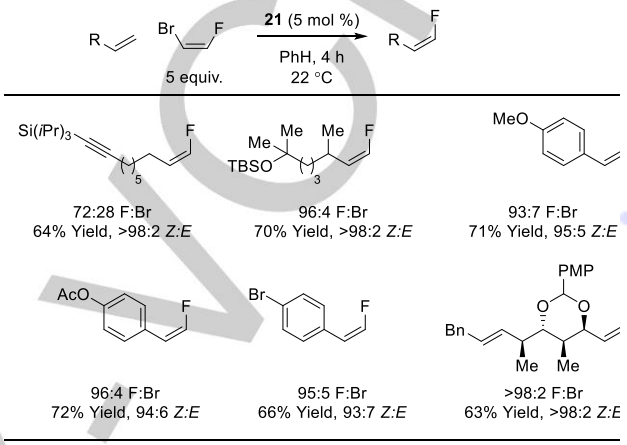


Figure 13. Employment of **21** in the formation of *Z*-alkenyl fluorides *via* stereoretentive cross metathesis.

Improvements to **21** were needed to promote the efficient and selective cross metathesis of *Z*-1,2-dichloroethene with aryl olefins and dienes, substrates found to be a problem in the aforementioned report.[86] Studies aimed at better understanding the catalytic intermediates during these transformations led to the discovery of a molybdenum catalyst with bromide incorporation.[100] Further investigations indicated a chloride-substituted molybdenum aryloxy catalyst, **22**, easily performed the cross metathesis of these problematic substrates (Figure 14).[100,101]

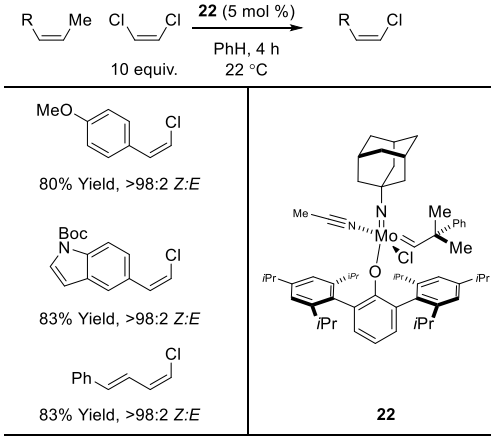


Figure 14. Employment of **22** in the formation of previously difficult to access *Z*-alkenyl chlorides *via* stereoretention.

Schrock, Hoveyda, and coworkers were also interested in *Z*-1,1,1,4,4,4-hexafluoro-2-butene as a cross metathesis

partner.[100] Employment of hexafluorobutene would allow access to a wide scope of substrates that possess a trifluoromethyl group, privileged molecules in the pharmaceutical and agrochemical industries.[98,99] Moreover, the synthesis of trifluoromethyl substituted olefins is limited, with these methods providing poor stereoselectivity or the thermodynamically favored *E*-product.[102–107] Common molybdenum and ruthenium catalysts provided no desired cross metathesis, due to the relative inertness of this electron deficient and hindered olefin. When employing **22** in the cross metathesis of hexafluorobutene and methyl oleate, the desired product was obtained in good *Z*-selectivity, but only in modest yields. Additional modifications to the imido group led to catalyst **23**, which furnished the desired product in 90% yield and 98:2 *Z*:*E*. Further examining the scope of **23** provided access to a variety of *Z*-trifluoromethyl substituted olefins. Catalyst **23** exhibited incredible functional group tolerance, performing cross metathesis with olefins containing protected alcohols, esters, allyl groups, aromatics, and heteroaromatics (Figure 15). Highly functionalized, biologically active precursors would also participate in cross metathesis with hexafluorobutene using **23** (Figure 15). Computational studies attribute the activity and selectivity of the chloride-bound catalyst to enhanced Lewis acidity of the molybdenum center and reduced steric repulsion between substituents in the metallacycle intermediate.

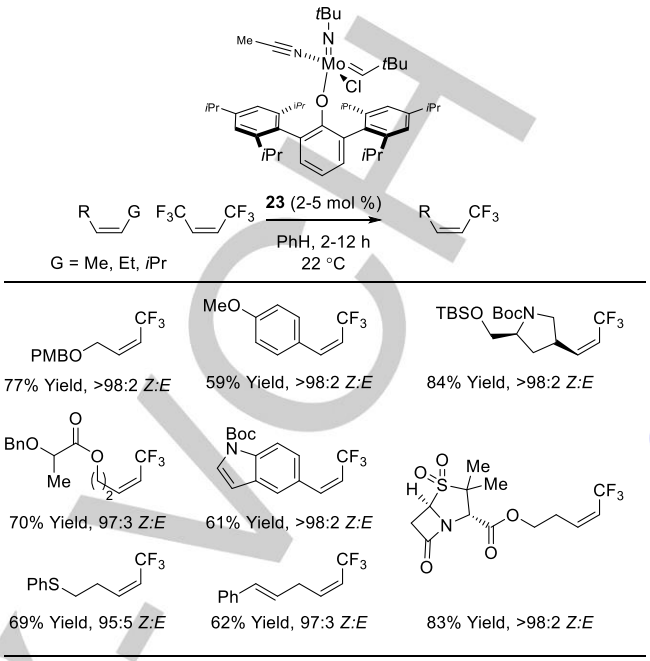


Figure 15. Employment of **23** in the formation of *Z*-trifluoromethyl substituted olefins *via* stereoretentive olefin metathesis.

5.2. *E*-Selectivity Through Stereoretention

Building on the success of stereoretentive olefin metathesis using *Z*-olefins, Schrock, Hoveyda, and coworkers investigated a pathway to a kinetically *E*-selective olefin metathesis through stereoretention of the olefins using molybdenum catalysts.[108] Initial studies were directed at formation of *E*-alkenyl halides[108] (it is known that alkenyl halides thermodynamically favor the *Z*-isomer owing to hyperconjugation of the C–H σ-bond to the C–halogen σ*[44]). Employment of **21** in the cross metathesis of *E*-1,2-dichloroethene and a terminally unsaturated silyl ether provided the desired product in 70% yield and 80:20 *E*:*Z* (Figure 16).

Further modification of the catalyst involved removing the *ortho*-substituents on the terphenyl rings, decreasing the steric

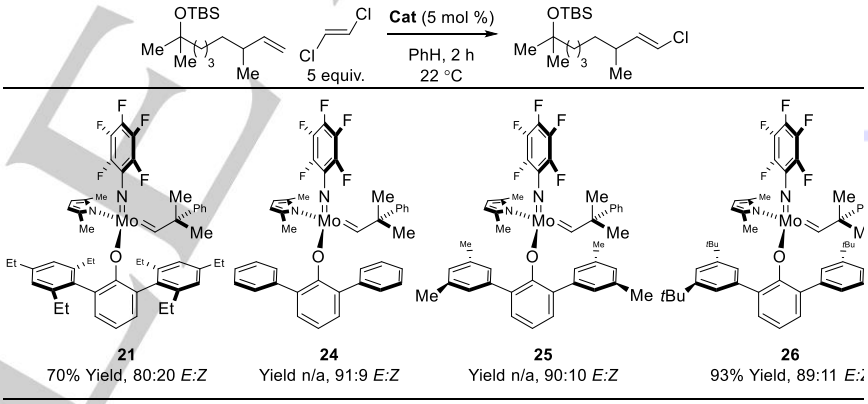


Figure 16. Assay of catalysts in the formation of *E*-alkenyl chlorides.

demands surrounding the metal center. Catalyst **24** provided the desired product in higher *E*-selectivity, but lower yield (Figure 16). Addition of substituents to the *meta*-positions (**25** and **26**) of the terphenyl groups increased both selectivity and catalyst stability (Figure 16). Catalyst **26** performed the cross metathesis between *E*-1,2-dichlorobutene and a variety of olefins. Cyclohexyl, aromatic, and heteroaromatic terminal olefins all participated in the cross metathesis furnishing the desired products in good yield and high *E*-selectivity (Figure 17). Unhindered aliphatic olefins performed less efficiently, providing the desired product in good yields but modest *E*-selectivity (Figure 17). It is believed that non-selective dimerization and competitive product isomerization can account for this effect.

Use of *E*-1,2-disubstituted olefins can circumvent this issue, providing a route to highly functionalized products in good yield and high *E*-selectivity.

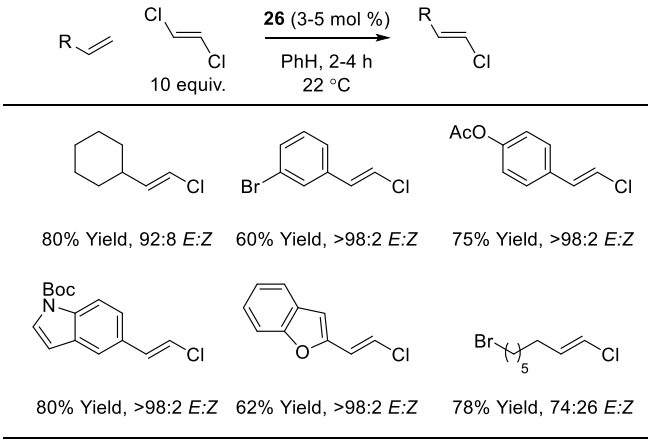


Figure 17. Employment of **26** in the formation of *E*-alkenyl chlorides *via* stereoretentive olefin metathesis.

The design of **26** is important to consider. The metallacyclobutane must be in an *anti*-arrangement, which is favored due to the mitigation of eclipsing interactions between the substituents on the metallacyclobutane (Figure 18, **XII** vs. **XIII**). However, this arrangement forces the substituent at C_3 toward the large aryloxy ligand. By removing the *ortho*-substituents on the terphenyl groups in **21**, this area is opened in **26** to accommodate the chloride at C_3 (Figure 18, **XII**). Additionally, the *meta*-substituents on the terphenyl will clash with the chloride at C_4 in **XIII**, disfavoring this species (Figure 18).

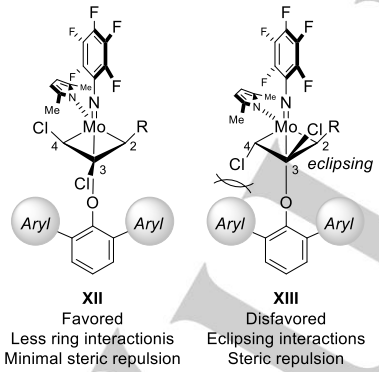


Figure 18. Design of stereoretentive metathesis catalyst for the formation of *E*-alkenyl chlorides.

Continued examination of this catalytic system led to the idea that steric demands for the substituent at C_3 could be used to develop a product-selective olefin metathesis using an unsymmetrical halo-ethene. *E*-1-Chloro-2-fluoroethene was employed as the unsymmetrical olefin, which could furnish two different metallacyclobutanes (Figure 19 (a)). It was proposed that **XIV** would be more favored than **XV** because there would be less steric repulsion with the fluoride pointed down toward the large aryloxide than with the chloride. This would allow access to *E*-alkenyl fluorides. Considering the importance of alkenyl fluorides, a kinetically *E*-selective process[108] would complement the methods previously developed forming *Z*-alkenyl fluorides[86] and *Z*-trifluoromethyl substituted olefins.[100]

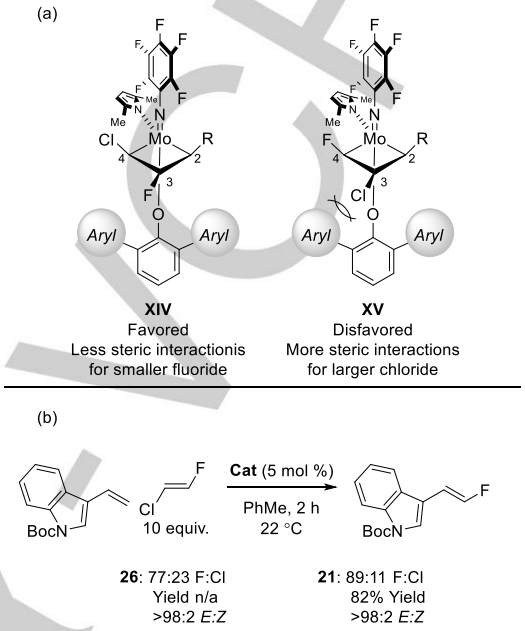


Figure 19. Studies on the formation of *E*-alkenyl fluorides *via* stereoretentive olefin metathesis. (a) Catalyst design to select for fluoro-containing products. (b) Cross metathesis showing larger aryloxy groups give better selectivity for the fluorinated product.

Cross metathesis between *N*-Boc-3-vinylindole and *E*-1-chloro-2-fluoroethene was performed with **26**. The fluorinated product was isolated in high *E*-selectivity but in a 77:23 ratio to the chlorinated product (Figure 19 (b)). A cross metathesis using **21** was attempted, as **21** has larger steric demands surrounding the metal center due to the *ortho*-substitution on the terphenyl group. Catalyst **21** generated the desired product, favoring the fluorinated product in an 89:11 ratio (Figure 19 (b)). Catalyst **21** displayed a wide substrate tolerance, performing the metathesis on alkyl, aromatic, and heteroaromatic functionalized olefins, selectively generating the desired fluorinated product in good yield and high *E*-selectivity.

Schrock, Hoveyda, and coworkers also investigated kinetically *E*-selective macrocyclic ring-closing metathesis (mRCM) using **26**.[109] Initial studies focused on using a diene with one of the olefins being an *E*-chloro-olefin, building on the previous success with chlorinated olefins in stereoretentive olefin metathesis. However, low turnovers were observed. It is believed that the chloro-alkylidene generated in the metathesis is of low stability, and because mRCM's are performed under dilute conditions, the alkylidene decomposes before it can react with another olefin. Previous studies showed that pinacolatoboryl- (B(pin)) substituted alkylidenes were less reactive than their carbon counterparts,[110] so these were

assayed in the mRCM using **26**. Macrocycles of various sizes were synthesized in moderate yield and high *E*-selectivity using **26** and B(pin)-substituted precursors (Figure 20). Furthermore this method was applied to the synthesis of recifeiolide[111–113] and pacritinib[114–117] (Figure 20).

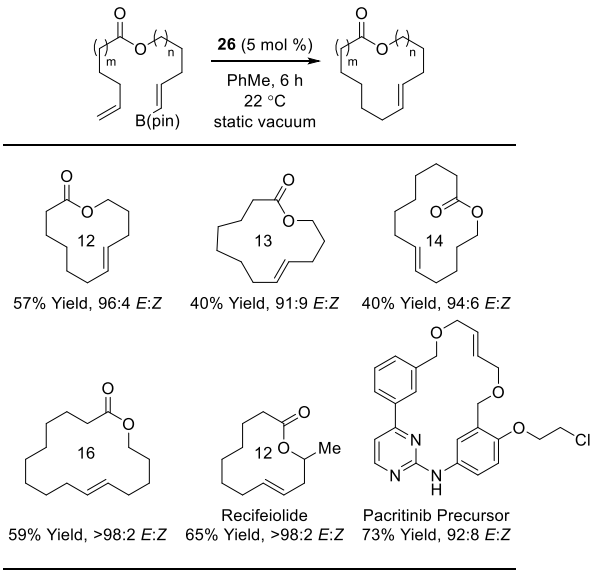


Figure 20. Employment of **26** in stereoretentive mRCM's to form *E*-macrocycles.

6. Summary and Outlook

Evidence for a stereoretentive pathway was apparent in early metathesis studies; however well-defined catalytic scaffolds to promote stereoselective olefin metathesis were unavailable. Since, stereoselective olefin metathesis has become ubiquitous as new catalysts that exhibit high degrees of control over the geometry of the key metallacyclobutane intermediate were developed. This has led to the emergence of highly active *Z*-selective catalysts based on molybdenum, tungsten, and ruthenium. Mechanistic investigations into the catechothiolate-modified ruthenium systems revealed that their *Z*-selectivity was a result of stereoretention. Exploitation of this stereoretentive pathway was also used to deliver a kinetically selective route to *E*-olefins. *Z*-selective molybdenum catalysts provided inspiration for the development of stereoretentive molybdenum catalysts, which allowed access to *Z*- and *E*-alkenyl halides through stereoretention. While stereoretention was observed in early studies of olefin metathesis, it has only recently been utilized as a reliable means of selectively controlling olefin geometry. Continued efforts in stereoretentive olefin metathesis will examine more robust catalytic scaffolds, ultimately leading to the discovery of a kinetically *E*-selective pathway for coupling terminal olefins.

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Keywords: olefin metathesis • stereoretention • tungsten • ruthenium • molybdenum

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